EXHIBIT B: CLEAN VERSION OF PARAGRAPHS IN THE SPECIFICATION
U.S. APPLICATION SERIAL NO. To be assigned
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(as amended April 2, 2001)

Paragraph at page 3, lines 7-14:

In a clinical setting, a physician must select, among several drugs, the most effective and safe drug for the patient. In making this decision, the physician needs to know how an particular patient may respond to a drug. One approach to individualized therapy decision making is through pharmacogenetics which relates individual variation in drug response to genetic variations. Pharmacogenetics promises a better understanding of the relationship between genetic variation and drug responses. However, so far, it has only provided limited information related to about 50 - 100 known drug metabolizing genes. In addition, pharmacogenetics does not address a patients' physiological or pathological conditions.

Paragraph at page 11, lines 14-19:

Biological pathways, particularly pathways involved in drug actions, *i.e.*, pathways that originate at a drug target (*e.g.*, proteins) and/or are hierarchical, can be identified for use in this invention by several means. Such means for identifying such pathways have been described, in detail, by Stoughton and Friend, U.S. application Serial No. 09/074,983, filed on May 8, 1998, now U.S. Patent No. 5,965,352, and Stoughton and Friend, U.S. application Serial No. 09/179,569, filed on October 27, 1998, which are incorporated herein by reference in their entireties.

Paragraph at page 12, lines 30-35:

The method of invention is based upon the ability to analyze the response of a biological system to the response of pathways. One particularly useful method for decomposing the drug response is by comparing measurements of changes in the biological state of a cell in response to graded drug exposure with measurements of changes in the biological state of biological pathways that are likely to be involved in the effects of the drug, the changes being in response to graded perturbations of these pathways.

Paragraph at page 24, lines 11-24:

In general, horizontal scaling is expected to be necessary. As discussed above, such scaling is necessary because values of the perturbation control parameters for the various candidate biological pathways are likely not to cause saturation responses at the same numerical perturbation control values nor at the same numerical value as the saturation response of the drug exposure. For example, the pathway perturbations may act according to such entirely different mechanisms as the titration of a viral transfection vector expressing a protein from which a pathway originates, or the control parameter of a controllable promoter controlling expression of an originating protein, or the exposure level of a drug of specific known action on an originating protein. The saturating control values of these mechanisms, and indeed their kinetic characteristics, are likely to be all unrelated. All of these mechanisms may be different from the action of the drug of interest. For example, where perturbation action on a cellular constituent from which a pathway originates can be modeled as a Hill function, there is no reason that the various "u_0" parameters will be the same.

Paragraph at page 25, lines 3-19:

More general horizontal scaling transformations are characterized by additional parameters. Flexible scaling transformations are possible with a number of parameters small enough, even though nonlinear, to be usefully employed in the minimization procedure of step 504. Multiple scaling parameters for the i'th pathway are represented herein by "α_i". Another example of a scaling transformation is a polynomial expansion generalizing the linear transformation of Eqn 3. A simple example of a more general scaling transformation is the previously described Hill function employed according to the following equation.

$$p_{i,l} = \frac{\alpha_i (t_l/\mu_i)^{n_i}}{1 + (t_l/\mu_i)^{n_i}} \qquad (4)$$

Again, Eqn. 3 provides the perturbation control value in the i'th pathway corresponding to the l'th drug exposure level and is parameterized for each pathway by the three parameters α_i, μ_i, and n_i. The Hill function scaling is more general at least in that it reduces to a linear scaling when n_i is 1 and t_l is much less than μ_i.

Paragraph at page 29, lines 27-34:

According to the preferred method, a residual distribution is constructed by repetitively solving Eqn. 5 with randomized input data and accumulating the residuals to form the empirical residual distribution. Thereby, the constructed empirical residual distribution arises from random data that has the same population statistics as the actual data. In detail, first, either the drug response data or the pathway response data (but not both) are randomized in step 505 with respect to the drug exposure levels or the perturbation control parameters, respectively. This randomization transformation is represented by the following transformation.

Paragraph at page 30, lines 5-13:

In Eqn. 10, Π represents a permutation independently chosen for each cellular constituent. Either the drug response or the each pathway response (but not both) is randomized according to Eqn. 10. Accordingly, the randomized drug or pathway response data are derived from the measured data by independent permutations of the measurement points. Second, Eqn. 5 is then solved by the chosen numerical approximation technique in step 504 and the value of the resulting residual saved. These steps are repeated for enough randomizations to construct a sufficiently significant expected probability distribution of residuals. In order to obtain confidence levels of 99% or better (*i.e.*, a P-value less than 0.01), then more than 100 randomizations are needed.

Paragraph at page 35, lines 19-25:

Where $D_k(t_l)$ is the drug activity on cellular constituent k when the drug is applied at a level t_l ; $R_{i,k}(\alpha_i, t_l)$ is the response of cellular constituent k in pathway i under perturbation (α_i, t_l) (for the scaling transformation of perturbation levels using parameter $\alpha_{i,}$ see section 5.1, *supra,* or U.S. Patent Application Ser. No. 09/074,983, filed on May 8, 1998, now U.S. Patent No. 5,965,352, previously incorporated by reference). $R_{i,k}(\alpha_i, t_l)$ represents the drug activity on the cellular constituent in pathway i. Drug activity on a cellular constituent k in pathway i is represented as:

$$D_{i,k}(t_l) = R_{i,k}(\alpha_i, t_l) \qquad (17)$$

Paragraph at page 35, line 33 through page 36, line 16:

For some embodiments of the invention, the drug activity on a particular pathway is more conveniently represented by a single parameter, rather than a group of responses of cellular constituents. In some preferred embodiments, the drug activity on pathway *i*, when the drug is applied at the level t_l, is represented by:

$$D_i(t_l) = \sum_k \beta_k R_{i,k}(\alpha_i, t_l) \qquad \textbf{(18)}$$

Where β_k is a constant for cellular constituent *k*. One of skill in the art would appreciate that the selection of constant β_k is dependent upon the unit used in measuring cellular constituent responses. For example, if a cellular constituent response measurement is the activity of an enzyme, while another cellular constituent response measurement is a gene expression ratio, two different β constants can be assigned to the two different cellular constituent types to adjust the difference in units and ranges of the measurements. Selection of the constants in a linear transformation to take account for different units of measurements and different range of variables is well within the skill of those in the art. In one particularly preferred embodiment, where the response of all cellular constituents are measured as the expression ratios (expression under perturbation over expression without perturbation), the β_k is given the value of 1.

Paragraph at page 37, lines 22-34:

One aspect of the invention provides methods for determining the specificity index (SI) of a drug in an *in vitro* system, based upon the drug's activity on target versus off-target pathways. The target and off-target pathways are previously discussed, for example, in Section 5.1, *supra*. The specificity index measurements is particularly useful to evaluate the relative efficacy and toxicity of a drug candidate during the early phase of drug screening. Specificity index is defined herein as the relative activity of a drug against its primary target pathway versus its activity against "off-target" pathways. Methods for determining the activities of a drug on different pathways have been described in detail in the Sections 5.1 and 5.2, *supra*. Some of the methods are also described in Stoughton and Friend, Methods for Identifying Pathways of Drug Action, U.S. Patent Application Ser. No. 09/074,983, filed on May 8, 1998, now U.S. Patent No. 5,965,352, incorporated previously by reference for all purposes. One of skill in the art would appreciate that the some methods of the invention are limited by particular methods for detecting "on-target" or "off-target" activities of a drug.

Paragraph at page 39, lines 10-13:

Even though it may be difficult to extrapolate a therapeutic index obtained from a model organism to the human or other target systems, the therapeutic index of a particular drug candidate relative to alternative drugs should be indicative of the ranking of those drugs in the target systems, especially when off-target effects of those drugs are similar.

Paragraph at page 39, lines 14-23:

In one preferred method, the threshold is set according to the relationship between toxicity and the pathways involved. For example, if a particular concentration of a drug that induces a particular off-target pathway by two-fold in a model system (such as a yeast model system) and later the drug is found to have toxicity when administered to a patient population at a dose that is equivalent to the concentration, the toxicity threshold may be set as two fold induction for this particular pathway. Similarly, if a particular concentration of a drug that represses a particular target pathway by three folds in a model system and later the drug is found to have a desired therapeutic effect in a patient administered with a dose that is equivalent to the concentration, the therapeutic threshold can be set as three-fold of repression for the particular target pathway.

Paragraph at page 39, line 28 through page 40, line 2:

Example 1 (Section 6, *infra*) illustrates one such embodiment. In this example, the expression of a number of genes are monitored as a wild type yeast culture is subjected to a graded levels of the drug FK506 (Fig. 8A). Similar experiments are repeated with a yeast culture whose CNA1 and CNA2 genes are deleted (Fig. 8B). CNA1 and CNA2 are two components of the calcineurin multi-protein complex. Because the drug FK506 acts upon the calcineurin protein to exert its activity on the calcineurin pathway. Deletion of CNA1 and CNA2 eliminates the primary target pathway for FK506. For a discussion of the yeast model system, see, Cardens et al., 1994, "Yeast as Model T Cells, Prosp. In DRUG DISCOVER. DESIGN, 2:103-126.

Paragraph at page 40, lines 19-24:

As discussed in the background section, clinical toxicity signs are difficult to detect. Drug effect or toxicity may not show up as clinical signs before it is too late to make a

informed therapeutic decision. The drug response of at least some pathways, however, are relatively faster. Accordingly, this invention provides methods for evaluating the drug effect or toxicity in a patient that undergoes drug therapy using pathway activities rather than clinical signs or individual cellular constituent changes.

Paragraph at page 40, lines 24-33:

In some embodiments, the expression of a large number of genes in the patient (a human or an animal) is determined while the patient undergoes therapy. The drug responses of the primary target pathway and off-target pathways are determined according to the methods of the invention and other suitable methods. If a patient's primary target pathway does not respond to the drug therapy and/or the off-target pathways respond strongly to the drug therapy, the therapy may be discontinued in favor of alternative treatments. Because the drug response of pathways can sometimes be determined earlier than clinical signs, the method of the invention offers the advantage that clinical decision can be made before clinical toxicity and therapy failure is detected by clinical signs.

Paragraph at page 41, lines 5-12:

In some embodiments, the expression of a large number of genes in a patient is monitored as the patient receives a plurality of perturbations. The perturbation can be a particular drug given at different doses. The drug responses of the target and off target pathways are determined according to the method of invention and other suitable methods. Suitable dosage can be determined so that the drug elicits a strong drug response in the target pathways and a relatively weak response in the off-target pathways. If a strong response in off-target pathways is illicit, the drug is determined to be unsuitable for the particular patient.

Paragraph at page 45, lines 5-15:

Figs. 8A-C illustrate the drug response data generated by a series of FK506 exposures. The horizontal axis is concentrations of the FK506 in logarithmic scale and the vertical axis is the values of the logarithm of the expression ratio of the genes most affected by FK506 on the vertical axis. Fig. 8A shows the transcriptional response of the yeast genome to a titration of the drug FK506. Fig. 8B shows the transcriptional response in a different experiment when the drug is applied to a yeast strain in which both components of the calcineurin protein

have been removed by deletion of the genes CNA1 and CNA2. Plotted genes have P-Value < 0.03 and abs(Log10(expression ratio)) > 0.3 at two or more concentrations in the series. P-Value is the probability that the up or down regulation is due to measurement error, as determined from observed statistics of the errors in Log10(expression ratio).